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Summary Review of Health Effects Associated with Ammonia Health Issue Assessment

Dynamac Corp., Rockville, MD

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16. ABSTRACT

Ammonia is a colorless gas with a repellent odor. It is a naturally occurring compound in the environment; however, it is also released into the environment from ammonia production facilities and during the manufacture and use of ammonia-containing products. It is a central compound in the environmental cycling of nitrogen and is involved in major processes such as mineralization, nitrification, and nitrogen fixation. Ammonia is a key metabolite in mammals and plays an essential role in acid-base regulation and biosynthesis of purines, pyrimidines, and nonessential amino acids. However, ammonia is a toxic gas and in experimental animals, effects from acute exposure to ammonia gas have ranged from mild irritation of the respiratory system and mucous membranes to convulsions, acute pulmonary edema, coma, and death. Continuous or repeated exposure of animals to sublethal concentrations of ammonia gas have produced adverse effects on the respiratory tract, liver, kidneys, and spleen. Quantitative data on the toxic effects of ammonia in humans is limited. Accidental exposure of humans to unspecified concentrations of ammonia has resulted in burns of the eyes, skin, and respiratory tract and in death. Chronic exposure of humans to low concentrations of ammonia has resulted in headache, nausea, and reduced appetite. A definite conclusion regarding the possible reproductive/teratogenic, mutagenic, or carcinogenic potential of ammonia cannot be drawn because of lack of adequate studies.

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Summary Review of Health Effects Associated with Ammonia

Health Issue Assessment

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Research Triangle Park, NC 27711

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Preface

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a source document for EPA use. The summary health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of ammonia as a hazardous air pollutant.

In the development of the assessment document, the scientific literature has been inventoried through January 1989, key studies have been evaluated, and summary conclusions have been prepared so that the chemicals' toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, considerable effort will be undertaken to obtain appropriate information regarding sources, emissions, and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

Abstract

Ammonia is a colorless gas with a repellent odor. It is a naturally occurring compound in the environment, however, it is also released into the environment from ammonia production facilities and during the manufacture and use of ammonia-containing products.

Ammonia is a central compound in the environmental cycling of nitrogen and is involved in major processes such as mineralization, nitrification, and nitrogen fixation. In the atmosphere, ammonia may undergo many transformations and is expected to have a relatively short residence time of 5 to 10 days.

Ammonia is a key metabolite in mammals and plays an essential role in acid-base regulation and biosynthesis of purines, pyrimidines, and non-essential amino acids. However, ammonia is a toxic gas and in experimental animals, effects from acute exposure to ammonia gas have ranged from mild irritation of the respiratory system and mucous membranes to convulsions, acute pulmonary edema, coma, and death. Continuous or repeated exposure of animals to sublethal concentrations of ammonia gas have produced adverse effects on the respiratory tract, liver, kidneys, and spleen.

Quantitative data on the toxic effects of ammonia in humans is limited. Accidental exposure of humans to unspecified concentrations of ammonia has resulted in burns of the eyes, skin, and respiratory tract and in death. Chronic exposure of humans to 40 ppm ammonia has resulted in headache, nausea, and reduced appetite. A definite conclusion regarding the possible reproductive/teratogenic, mutagenic, or carcinogenic potential of ammonia cannot be drawn because of the lack of adequate studies.

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Authors, Contributors, and Reviewers

The following personnel of Dynamac Corporation were involved in the preparation of this document: Finis Cavender, Ph.D. (Department Director); Nicolas P. Hajjar, Ph.D. (Project Manager/Principal Author); Dana Cazzulino; Cyrus Hamidi; Yvonne Jones-Brown, Ph.D.; Lawrence Kaufman, Ph.D.; Leonard Keifer, Ph.D.; and Kumar D. Mainigi, Ph.D. (Authors); William McLellan, Ph.D. (Reviewer); Anne Gardner (Technical Editor); and Gloria Fine (Information Specialist). This document was prepared under contract with the Environmental Criteria and Assessment Office, EPA, Research Triangle Park, NC (Beverly Comfort, Project Manager).

This document has been reviewed for scientific and technical merit by the following scientists: Professor William J. White, Department of Comparative Medicine, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA, 17033; Professor I. W. Waters, Research Institute of Pharmaceutical Sciences, University of Mississippi, University, MS 38677; Dr. D. Burrows Schaub, Burrows Associates, Ltd., Fredrick, MD 21701. In addition, it has been reviewed by members of the Human Health Assessment Group (HHAG) and the Exposure Assessment Group (EAG) of the Office of Health and Environmental Assessment (OHEA), EPA, Washington, DC.

1. Summary and Conclusions

Ammonia (CAS No. 7664-41-7) is a colorless gas with a repellent odor. It is very soluble in water with a high vapor pressure and a low vapor density. Ammonia was ranked fourth among the chemicals produced in the United States in 1987. It is used in the manufacture of fertilizers, fibers and plastics, and explosives.

Ammonia is released into the environment from ammonia production facilities via industrial gaseous emissions and aqueous waste streams as well as during the manufacture and use of ammonia-containing products. It is also a naturally occurring compound and a product of animal, fish, and microbial metabolism. Ambient air concentrations range from 0.1 to 9.0 $\mu g/m^3$, although higher levels may be found in the vicinity of point sources.

The Occupational Safety and Health Administration has established an 8-hour TWA permissible exposure limit for ammonia of 50 ppm (35 mg/m^3). Analytical methods used to determine ammonia include colorimetry, titrimetry, conductimetry, specific ion electrode, ion chromatography, chemiluminescence, absorption spectroscopy, gas chromatography, and mass spectrometry.

Ammonia is a central compound in the environmental cycling of nitrogen and is involved in major processes such as mineralization, nitrification, and nitrogen fixation. Under most environmental conditions, the ammonium ion (NH_4^+) is expected to predominate. The ammonium ion is less mobile than unionized ammonia (NH_3) in soil and water. In the atmosphere, ammonia may undergo many transformations and is expected to have a relatively short residence time of 5 to 10 days. The most important transformation is its solution in water droplets together with sulfur dioxide or other gases to form aerosols, with up to 75 percent removal by rainout.

Ammonia is moderately toxic to aquatic organisms and is more toxic than the ammonium ion. The acute toxicity of unionized ammonia to fish has been extensively studied. The 24- and 96-hour acute LD_{50} values for fish range from 0.07 to 12.7 mg/L, with salmonid species generally being more sensitive. Aquatic invertebrates have a range of sensitivity comparable to that of fish and show a varying sensitivity with developmental stages.

Ammonia gas is readily absorbed through the lungs as indicated by increased ammonia concentrations in the blood following exposure. However, the increase in blood levels is not exposure-related, so that only modest increases are noted at higher exposures. Retention of ammonia in the respiratory tract of dogs exposed to 450 to 1,500 ppm and humans exposed to up to 500 ppm is $\geq$ 80 percent. Following absorption, ammonia is incorporated into the amino acid pool and other organic molecules. However, the route of administration drastically alters the distribution of ammonia between alpha-amino, amidine, and amide nitrogen of organ proteins. Ammonia is metabolized largely by pathways involving hepatic glutamic dehydrogenase and carbamyl synthetase following intragastric and intraperitoneal administration, whereas the glutamic synthetase route is involved following subcutaneous and intravenous administration. Approximately 90 percent of

^{15}N-labeled ammonia administered intravenously to rats was incorporated into glutamic amide nitrogen (80 percent) and urea (10 percent). Low levels of labeled ^{15}N (expressed as glutamine and ureas) were found in various tissues and organs. Ammonia is excreted as urea in mammals, but excretion was also found to occur via the lungs in expired air of several experimental animals and human subjects exposed to NH_3 vapor or injected intravenously with ammonia acetate.

Ammonia is a key metabolite in mammals and plays an essential role in acid-base regulation and biosynthesis of purines, pyrimidines, and nonessential amino acids. Elevated levels of endogenous ammonia resulting from metabolic and genetic disease have caused liver failure, neurologic disorders, and encephalopathy. There is no information on the potential risk to humans with genetic or metabolic disorders as a result of exposure to exogenous ammonia. In experimental ammonia toxicity studies with animals, alteration in metabolic and functional aspects of the brain, changes in neurotransmitter levels, involvement of glial cells, and alterations in the blood-brain barrier have been noted.

Ammonia is a toxic, gaseous compound at relatively moderate concentrations. In animals, compound- and concentration-related effects of acute exposure to ammonia gas progress from mild irritation of the respiratory system and mucous membranes to convulsions, acute pulmonary edema, coma, and death. The acute inhalation LC_{50} values for a 60-minute exposure period are 4,230 ppm in mice and 14,140 and 19,770 ppm in male and female rats, respectively. The data on acute exposure to low levels of ammonia are conflicting; however, no signs of irritation or histological changes were seen in the respiratory tract of rats exposed to 4 ppm ammonia for up to 7 days. Continuous or repeated exposure of animals to sublethal concentrations of ammonia has produced adverse effects in the tissues of the respiratory tract, liver, kidneys, and spleen. It may also increase the tendency towards, and/or severity of, respiratory tract infections by reducing tracheal ciliary activity and the phagocytic activity of pulmonary alveolar macrophages and may produce anorexia. No clinically significant effects were noted in rats, guinea pigs, rabbits, dogs, or monkeys continuously exposed to ammonia at a concentration of 57 ppm for 114 days.

No adequate information was found on the effects of chronic exposure to ammonia in animals. Ammonium hydroxide administered in drinking water to Swiss mice at levels of 0.1, 0.2, or 0.3 percent or to C3H mice at a level of 0.1 percent was not carcinogenic. In another study a significant increase in lung tumors was not found in mice after administration of 42 mg/kg ammonia twice a week for 4 weeks. Limited data suggest that ammonium hydroxide may be mutagenic to *Escherichia coli* and *Drosophila melanogaster*. Ammonium chloride was also found to reduce multiplication of 3T3 and SV-40 transformed 3T3 mouse fibroblasts. Teratogenicity or reproductive studies in mammals were not reported for ammonia in the available literature. Additional data are needed to determine the chronic effects and mutagenic, teratogenic, and reproductive potential of ammonia.

Accidental exposure of humans to unspecified concentrations of ammonia has resulted in burns of the eyes, skin, and respiratory tract and in death. Both immediate and long-term effects have been associated with ammonia exposure. Chronic exposure to 40 ppm ammonia vapor has resulted in headache, nausea, and reduced appetite. In experimental studies, hyperventilation, lacrimation, and nasal irritation were noted in subjects exposed at 500 ppm for 30 minutes, but no changes were noted for blood urea and nonprotein nitrogen, although increases in nonprotein nitrogen levels were

observed with longer (4-hour) exposure periods. In another study, exposure at concentrations of 50 ppm or less did not cause irritation or discomfort. In repeated exposure studies (25, 50, or 100 ppm for 6-hour sessions once a week for 6 weeks), no apparent changes were noted in respiratory rate, blood pressure, pulse, or forced vital capacity. The frequency of mild eye irritation decreased in the later sessions, suggesting adaptation. No adequate studies were found on the adverse effects of chronic occupational exposure to ammonia. Ammonia is classified as group D "not classifiable as to human carcinogenicity" based on the weight-of-evidence approach in the current EPA guidelines for carcinogen risk assessment.

2. Background Information

This overview provides a brief summary of the data available on the health effects from exposure to ammonia. Emphasis is placed on determining whether there is evidence to suggest that ammonia exerts effects on human health under conditions and at concentrations commonly experienced by the general public. Both acute and chronic effects are addressed, including general toxicity, teratogenicity, mutagenicity, and carcinogenicity. To place the health effects discussion in perspective, this report also reviews certain air quality aspects of ammonia in the United States, including sources, distribution, fate, and concentrations associated with rural, urban, and point-source areas.

2.1. Chemical Characterization and Measurement

Ammonia (CAS No. 7664-41-7) has the empirical and molecular formula NH_3. It is a colorless gas at room temperature with a sharp and repellent odor and a molecular weight of 17.03. Ammonia is very soluble in water (34 percent at 20°C or about 531 g/L at 20°C) and has a high vapor pressure (8.7 atm at 20°C) and a low vapor density (0.6 g/L) (TDB, Verschueren, 1983).

For determination of ammonia in air, it is first necessary to absorb the ammonia in a liquid. Sampling air for determination of trace amounts of ammonia has several inherent problems: minimization of human ammonia contamination, the propensity of ammonia to adsorb to all surfaces, especially at low concentrations, differentiation of aerosol ammonia and gaseous ammonia, and inefficiency of bubbler samplers. After sample collection, ammonia concentrations are determined by established methods including colorimetry, titrimetry, conductimetry, specific ion electrode, ion chromatography, chemiluminescence, absorption spectroscopy, or gas chromatography and mass spectrometry (National Research Council, 1977).

Ammonia is determined in water or wastewater using one of the standard methods developed for examination of water and wastewater, i.e., colorimetry, titrimetry, or the ammonia-selective electrode (Franson, 1981).

Variations of the basic methods have also been instituted in an effort to overcome difficulties inherent in the established methods. Such variations include automated colorimetry (Skjemstad and Reeve, 1978; Bos, 1980; Canelli, 1976), ion chromatography (Bouyoucos and Melcher, 1983), gas chromatography (Hutchinson et al., 1982), nonautomated colorimetry (Bower and Holm-Hansen, 1980; Boo and Ma, 1976; Hampson, 1977), specific ion electrode (Ferm, 1979), ring oven (Cattell and Du Cros, 1976), automated distillation-spectrophotometry (Crowther and Evans, 1980), chemiluminescence (McClenny and Bennett, 1980; Hales and Drewes, 1979), air sampling techniques (Braman et al., 1982), coated piezoelectric crystals (Guilbault, 1981; Hlavay and Guilbault, 1978), fluorescence (Abbas and Tanner, 1981; Aoki et al., 1983; Aoki et al., 1986), teflon beads (Harward et al., 1982), and harmonic diode laser system (Cappellani et al., 1985).

2.2. Sources and Emissions

Domestic production capacity of ammonia in 1984 was approximately 18 million tons (Chemical and Engineering News, 1985). As of March 1985, ammonia was produced domestically by 62 companies at 99 plant sites. Ammonia was ranked fourth among the chemicals produced in the United States in 1987 (Reisch, 1988) with a production volume of 17.2 million tons, an increase of 15.4 percent from 1986 (Reisch, 1988).

Ammonia is manufactured primarily by a modified Haber reduction method using atmospheric nitrogen and a hydrogen source (TDB). The major producers of ammonia in the U.S. are CF Industries, Columbia Nitrogen, Farmland Industries, Union Oil Company, and the Williams Companies (Agrico). Major end uses for ammonia are in the manufacture of fertilizer (80 percent), fibers and plastics (10 percent), and explosives (5 percent) (Chemical & Engineering News, 1985).

2.3. Environmental Release and Exposure

Ammonia is released into the environment from ammonia production facilities via industrial gaseous emissions and aqueous waste streams. It is also released during direct application of anhydrous ammonia and urea to soil (National Research Council, 1977; Denmead et al. 1982; Reynolds and Wolf, 1987), the production of urea and ammonium nitrate, application of animal waste as a fertilizer (National Research Council, 1977) and from animal feedlots (Hutchinson et al., 1982), vegetation decay (Alkezweeny et al., 1986), in process gas condensate from coal gasifiers (Hanson et al., 1985), and automobile exhausts (Pierson and Brachaczek, 1983).

Ammonia is a product of animal metabolism as well as a chemical that is manufactured and used in commerce. Ammonia is ubiquitous in the environment, existing in equilibrium in two forms, mostly as a result of the nitrogen cycle (Figure 2-1).

$$\underset{\text{Ammonium ion}}{NH_4^+} + H_2O \leftrightarrows \underset{\text{Ammonia}}{NH_3} + H_3O^+$$

Therefore, the fate of anthropomorphic ammonia in the environment should be considered in the context that the compound is central to the environmental cycling of nitrogen. A network of active and efficient, natural inorganic and organic processes has trapped, transformed, produced, and/or used ammonia before there were contributions from human sources. Consequently, the ammonia that enters the environment from human sources enters a system already adapted to the presence of ammonia and would be subject to the same processes as naturally occurring ammonia. Some of the major processes of the nitrogen cycle that involve ammonia include, with associated reactions (unbalanced), the following (National Research Council, 1977):

Mineralization:

$$\underset{\text{Organic nitrogen}}{RNH_2} + \underset{\text{Oxygen}}{O_2} \rightarrow \underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Water}}{H_2O} + \underset{\text{Ammonia ion}}{NH_4^+}$$

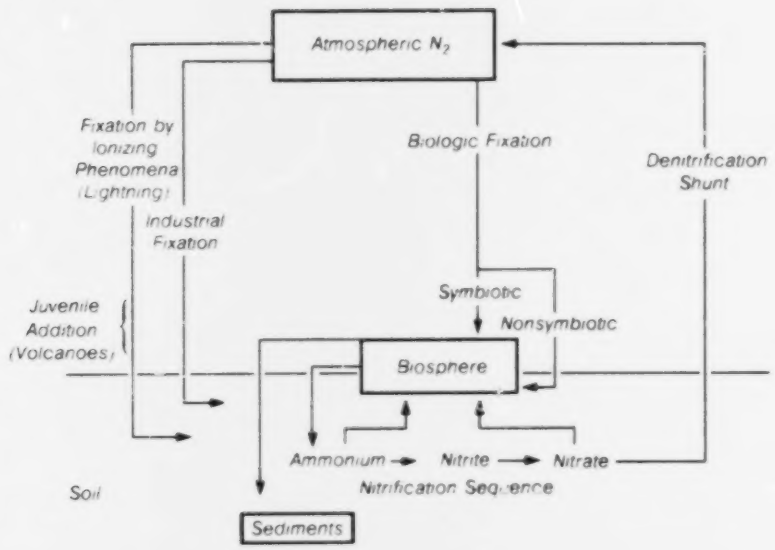

Figure 2-1. Generalized representation of the nitrogen cycle.
Source: National Research Council (1977).

Nitrification:

$$\underset{\text{Ammonium}}{NH_4^+} + \underset{\text{Oxygen}}{O_2} \rightarrow \underset{\text{Water}}{H_2O} + \underset{\text{Nitrite}}{NO_2^-}$$

Nitrogen fixation:

$$\underset{\text{Nitrogen gas}}{N_2} + \underset{\text{Organic matter}}{[HCHO]} \rightarrow \underset{\text{Ammonium ion}}{NH_4^+} + \underset{\text{Carbon dioxide}}{CO_2}$$

Ammonia is an important intermediate in the assimilation of nitrogen from the soil by plants. Nitrogen is present in the soil largely in the organic form. Before being assimilated by plants, it is normally mineralized by microbial processes. The formation of ammonium ion is the first step in the mineralization process. Most plants can assimilate ammonium ion, but the ammonium ion may also be oxidized to the nitrate ion, the most common form of mineralized nitrogen in soil, which may be assimilated by plants as well (Andersson and Hooper, 1983; Cullimore and Sims, 1981; Lemon and Van Houtte, 1980; Kholdebarin and Oertli, 1977; National Research Council, 1977).

Nitrification is a two-step, energy-yielding process exploited for metabolic energy by two specific genera of microorganisms. Ammonia is converted to nitrite by *Nitrosomonas*, and nitrite is converted to nitrate by *Nitrobacter*. This process occurs in soil and water (Andersson and Hooper, 1983; American Petroleum Institute, 1981; Kholdebarin and Oertli, 1977).

Another source of mineralized nitrogen is from nitrogen fixation, where gaseous nitrogen is transformed to ammonium ion, usually by metabolic processes. Nitrogen fixation occurs in blue-green algae and a few genera of microorganisms, which include aerobic organisms such as *Azotobacter* spp., anaerobic organisms such as *Clostridium* spp., and organisms in symbiotic association with higher plants such as *Rhizobium* spp. (Bailey and Ollis, 1977; National Research Council, 1977).

Industrial sources of ammonia are also a form of nitrogen fixation and are included in the nitrogen cycle shown in Figure 2-1. Because the nitrogen cycle is dynamic, no dramatic buildup of ammonia is expected to occur as a result of these additional inputs. Also, volatilization, adsorption, and chemical transformation will affect the fate of ammonia (American Petroleum Institute, 1981; Weiler, 1979; National Research Council, 1977).

In the atmosphere, ammonia may undergo many transformations and is expected to have a relatively short residence time of 5 to 10 days. Probably the most important removal mechanism is its solution in water droplets together with sulfur dioxide or other gases to form aerosols, with up to 75 percent removal by rainout and washout. The principal product formed is ammonium sulfate, but a number of secondary products can also be formed. Reactions of ammonia with nitric acid or nitrogen dioxide may yield other aerosols with the ammonium nitrate as the principal product. Other reactions of ammonia, such as with OH radical, yield NH_2 radical. The products of NH_2 radical reaction are not clearly known (Mearns and Ofosu-Asiedu, 1984; Tang, 1980; Doyle et al., 1979; Weiler, 1979; Esmen and Fergus, 1977; National Research Cancer, 1977).

Nitrification and volatilization are the important and competitive fate processes in surface waters. Volatilization rates are highest at the sources of industrial inputs of ammonia, whereas nitrification processes are more significant in lakes, slow moving rivers, and estuaries. Nitrification is responsive to high inputs of ammonia, although conditions of high nitrification may contribute to low levels of dissolved oxygen and the eutrophication of a body of water. Adsorption to particles may also play a role in the aquatic fate of ammonia. Once bound to a particle, ammonia may settle to the sediment where soil-type fate processes will take over (Orhon and Goneng, 1982; American Petroleum Institute, 1981; Bouwmeester and Vlek, 1981; Weiler, 1979).

In water, the ammonium ion is expected to be predominant; however, equilibrium is affected by pH and temperature. The fraction of ammonia increases tenfold with each unit increase in pH and increases to a lesser degree with increasing temperature (Erickson, 1985; Burkhalter and Kaya, 1977).

The general population may be potentially exposed to ammonia via inhalation of contaminated air from industrial plants, farms, and numerous other natural sources, including water supplies from wells. Ammonia has been detected in emissions from oil refineries at concentrations up to 470 mg/m^3 (U. S. Miner, 1969; National Research Council, 1977). Ammonia concentrations of 1,900 $\mu g/m^3$ and 42 $\mu g/m^3$ were measured in emissions from two pulverized-coal power plants (Bauer and Andren, 1985). Urban ammonia levels in air as high as 280 $\mu g/m^3$ have been measured in Italy, while an urban-

industrial area in Japan had ammonia levels of 7 to 210 $\mu g/m^3$ (National Research Council, 1977).

Several studies in California indicated measured ammonia levels of 3 to 60 $\mu g/m^3$. One sample in the vicinity of a dairy farm had an ammonia concentration of 315 $\mu g/m^3$. Hutchinson et al. (1982) reported that air samples taken 1.2 meters above a large cattle feedlot in Colorado contained ammonia levels ranging from 290 to 1,200 $\mu g/m^3$. Altezweeney et al. (1986) reported ambient ammonia concentrations of 0.04 to 5.6 $\mu g/m^3$ for the summer of 1983, in an area surrounded by horse and cattle farms near Lexington, KY. Ambient ammonia levels ranging from 6,500 to 29,800 $\mu g/m^3$ have been reported in confinement structures of swine-producing farms (Donham and Popendorf, 1985).

Ammonia levels in nonurban air samples in Seattle, WA have ranged from 2.0 to 8.0 $\mu g/m^3$ and urban air contained 0.8 to 77.0 $\mu g/m^3$. Ambient ammonia concentrations in coastal Virginia ranged from 1.4 to 3.5 $\mu g/m^3$ (Harward et al., 1982). Analysis of air samples from the Allegheny Mountain Tunnel in Pennsylvania for ammonia showed mean concentrations of 3.0 $\mu g/m^3$ in the tunnel and 0.44 $\mu g/m^3$ outside the tunnel (Pierson and Brachaczek, 1983) and air samples in a rural area in Pennsylvania have reportedly ranged from 0.01 to 0.137 $\mu g/m^3$ (Lewin et al., 1986). Analysis of air samples from Commerce City, CO, Abbeville, LA, and Luray, VA showed average ammonia levels of 2.4, 0.57, and 1.34 $\mu g/m^3$, respectively. Ambient ammonia levels ranging from 1.4 to 5.6 $\mu g/m^3$ were reported on a smoggy day in Los Angeles, CA (Hanst et al., 1982). Hunt et al. (1984) reported ambient ammonia levels ranging from 3.0 to 9.0 $\mu g/m^3$ in various locations in Texas. In air samples taken from June 1981 to June 1982 in Warren, MI, average ammonia levels ranged from 0.10 to 0.85 $\mu g/m^3$. The highest average annual ammonia level was found during the summer months (Cadle, 1985).

Ammonia may also be present in the atmosphere as particulate ammonium salts. In 1976 a mean ammonium level of 1.2 $\mu g/m^3$ was measured in Washington, D.C. (Kowalczyk et al., 1982). Urban ammonium concentrations ranging from 0 to 15.1 $\mu g/m^3$ were reported in 1968 for various air monitoring stations throughout the United States. Nonurban ammonium concentrations ranged from 0 to 1.2 $\mu g/m^3$ (National Research Council, 1977).

Ammonia concentrations in precipitation (the source of surface water) have averaged from 0.2 to 1.0 ppm in snow in the United States and Canada (Feth, 1966). Mean ammonium ion concentrations deposited in precipitation at three sites in Minnesota ranged from 33.6 to 47.9 $\mu eq/L$ (Munger, 1982). Ammonium ion concentrations in rain ranging from 0.5 to 28.0 ppm were reported for Israel and average yearly concentrations of 0.17 to 1.5 ppm were reported in Sweden. High ammonium ion concentrations have been measured in some natural waters, including levels up to 485 ppm in a group of California springs and 1,400 ppm in one hotspring.

Determination of the ammonium-nitrogen concentrations in groundwater, taken from wells located in North Carolina under various soil and crop conditions, ranged from 0.01 to 6.85 ppm with average quarterly levels of 0.01 to 5.10 ppm (Gilliam et al., 1974). Wells in Michigan contained an average of 0.18 ppm ammonia-nitrogen in a marshy environment and 0.16 ppm in an agricultural area. A sampling of water from four elementary school sites, each with a well for its water supply, indicated ammonia-nitrogen concentrations ranging from 0.01 to 0.57 ppm (Rajagopal, 1978). Ammonia-nitrogen concentrations as high as 38 ppm were measured in groundwater obtained from beneath corrals (Stewart et al., 1967).

Estimates of occupational exposures to ammonia have been reported in industrial hygiene surveys performed by the National Institute for Occupational Safety and Health (NIOSH). According to the National Occupational Hazard Survey (NOHS), 2,524,078 workers were potentially exposed to ammonia in domestic workplace environments in 1970. Preliminary data for 1980 in the National Occupational Exposure Survey (NOES) indicate that 417,358 workers, including 120,599 women, were exposed to the compound. Table 2-1 lists occupations having potential exposure to ammonia levels higher than that normally found in the environment.

Atmospheric workplace concentration limits have been established for ammonia. The Occupational Safety and Health Administration (Code of Federal Regulations, 1989) established an 8-hour time-weighted average (TWA) permissible exposure limit of 50 ppm (35 mg/m^3) for ammonia, and the American Conference of Governmental Industrial Hygienists (ACGIH, 1984) recommended an 8-hour TWA threshold limit value (TLV) of 25 ppm (18 mg/m^3) and a 15-minute short-term exposure limit (STEL) of 35 ppm (27 mg/m^3).

2.4. Environmental Effects

Ammonia is highly toxic to aquatic organisms, and its concentration in U.S. waters has been regulated to a maximum of 0.02 mg/L (as unionized ammonia) (U.S. Environmental Protection Agency, 1977). In aqueous solution, ammonia is present in unionized (NH_3) and ionized (NH_4^+) forms. The percentage of total ammonia present in the unionized form and its toxicity to aquatic organisms is highly dependent upon the pH and temperature of the media (Thurston et al., 1981c). As pH and temperature increases, the ammonia equilibrium is shifted toward the NH_3 chemical species (Emerson et al., 1975).

The acute toxicity of ammonia to fish has been studied extensively and is well summarized in the literature (Thurston et al., 1984; Ruffier et al., 1981; European Inland Fisheries Advisory Commission, 1973). The reported median lethal concentrations of unionized ammonia for 22 species of fish are given in Table 2-2.

Data on the effect of increasing water pH upon the toxicity of unionized ammonia are mixed. Thurston et al. (1984) reported increasing acute toxicity of unionized ammonia to rainbow trout as the pH increased to pH 7.5. Conversely, Broderius et al. (1985) reported decreasing toxicity of unionized ammonia to smallmouth bass as water pH increased from 6.55 to 8.71.

Limited data on the subacute and chronic effects of ammonia upon fish are available. The estimated 32-day no-observed-effect concentrations (NOEC) for growth effects in smallmouth bass are 17.4, 14.4, 14.6, and 2.4 mg/L total ammonia and 0.437, 0.148, 0.599, and 0.612 mg/L unionized ammonia at pH values of 6.60, 7.25, 7.38, and 8.68, respectively (Broderius et al., 1985). Exposure of carp fry (*Cyprinis carpio*) to 0.1 mg NH_3/L for 3 weeks resulted in significant ($p < 0.01$) changes in leukocyte, erythrocyte, and erythroblast counts as well as increases in brain and muscle free amino acid levels (Dabrowska and Wlasow, 1986).

Aquatic invertebrates are generally less sensitive than fish to exposure to ammonia. The reported median lethal concentrations of unionized ammonia for nine species of aquatic invertebrates are given in Table 2-3. Several studies show varying sensitivity with developmental stage (Watton and Hawkes, 1984;

Table 2-1. Occupations with Potential Exposure to Ammonia

Acetylene worker	Lacquer maker
Aluminum worker	Latex worker
Amine worker	Manure handler
Ammonia worker	Metal extractor
Ammonium salt maker	Metal-powder processor
Aniline maker	Mirror silverer
Annealer	Nitric acid maker
Boneblack maker	Organic-chemical synthesizer
Brazier	Paper maker
Bronzer	Perfume maker
Calcium carbide maker	Pesticide maker
Case hardener	Petroleum-refinery worker
Chemical-laboratory worker	Photoengraver
Chemical manufacturer	Photographic-film maker
Coal-tar worker	Plastic-cement mixer
Coke maker	Pulp maker
Coke-oven byproduct extractor	Rayon maker
Compressed-gas worker	Refrigeration worker
Corn grower	Resin maker
Cotton finisher	Rocket-fuel maker
Cyanide maker	Rubber-cement mixer
Decorator	Rubber worker
Diazo reproducing-machine operator	Sewer worker
Drug maker	Shellac maker
Dye-intermediate maker	Shoe finisher
Dye maker	Soda ash maker
Electroplater	Solvay-process worker
Electrotyper	Stableman
Explosive maker	Steel maker
Farmer	Sugar refiner
Fertilizer worker	Sulfuric acid worker
Galvanizer	Synthetic-fiber maker
Gas purifier	Tannery worker
Glass cleaner	Transportation worker
Glue maker	Urea maker
Ice cream maker	Varnish maker
Ice maker	Vulcanizer
Illuminating-gas worker	Water-base-paint worker
Ink maker	Water treater
Janitor	Wool scourer

Source: National Research Council (1977).

Armstrong et al., 1978; Jayasankar and Muthu, 1983; Reddy and Menon, 1979).

Ammonia can cause various kinds of injury to terrestrial plants including necrosis, growth reduction, and increased frost sensitivity. Growth reduction may result from uncoupling photophosphorylation, which lowers carbohydrate

Table 2-2. Acute Lethal Concentration Values for Ammonia in Fish

Organism	LC_{50} (mg/L)	Exposure conditions	Reference
A. FRESHWATER			
Abramis brama (Bream)	0.41	Static, asymptotic	Ball (1967)
Catastomus commerson (White sucker)	0.76-2.22	Flowthrough, 96 h Variable: temperature 3.6-15.3°C	Arthur et al. (1987)
Ictalurus punctatus (Channel catfish fingerling)	2.46	Flowthrough, 24 h	Robinette (1976)
I. punctatus (Channel catfish juveniles)	1.6-3.1	Flowthrough and static, 96 h	Colt and Tchobanoglous (1978)
I. punctatus (Channel catfish)	0.5-1.29	Flowthrough, 96 h Variable: temperature 3.5-19.6°C	Arthur et al. (1987)
Lepomis cyanellus (Green sunfish juveniles)	0.5-1.73	Flowthrough, 96 h Variable: pH 6.6-8.7	McCormick et al. (1984)
Micropterus dolomieui (Smallmouth bass juveniles)	0.694-1.78	Flowthrough, 96 h Variable: pH 6.53-8.7	Broderius et al. (1985)
M. treculi (Guadalupe bass fingerlings)	12.7	Static, 96 h	Tomasso and Carmichael (1986)
Oncorhynchus gorbuscha (Pink salmon eggs and larvae)	0.083	Flowthrough, 96 h	Rice and Bailey (1980)
O. kisutch (Coho salmon fingerlings)	0.45	Flowthrough, 96 h	Buckley (1978)
O. tschawytscha (Chinook salmon parr)	0.36	Static, 96 h	Harader and Allen (1983)
Perca flavescens (Perch)	0.29	Static, asymptotic	Ball (1967)
Pimephales promelas (Fathead minnow)	0.75-3.4	Flowthrough, 96 h Variable: temperature dissolved oxygen	Thurston et al. (1983)
Rutilus rutilus (Roach)	0.35	Static, asymptotic	Ball (1967)

(continued)

Table 2-2. Continued

Organism	LC_{50} (mg/L)	Exposure conditions	Reference
A. FRESHWATER (continued)			
Salmo clarki (Cutthroat trout adults)	0.30-0.33	Flowthrough, 96 h	Thurston et al. (1981a)
Salmo gairdneri (Rainbow trout)	0.41	Static, asymptotic	Ball (1967)
S. gairdneri (Rainbow trout end-of-yolk-sac fry)	0.072	Static, 24 h	Rice and Stokes (1975)
S. gairdneri (Rainbow trout fingerlings)	0.3-0.8	Flowthrough, 96 h Variable: dissolved oxygen 2.6-8.6 mg/L	Thurston et al. (1981b)
S. gairdneri (Rainbow trout fingerlings)	0.16-0.50	Flowthrough, 96 h	Thurston et al. (1981b)
S. gairdneri (Rainbow trout)	0.53	Flowthrough, 96 h	Arthur et al. (1987)
Scardinius erythropathalmus (Rudd)	0.36	Static, asymptotic	Ball (1967)
Stizostedion vitreum (Walleye)	0.66	Flowthrough, 96 h	Arthur et al. (1987)
Tilapia aurea (Tilapia)	2.4	Flowthrough, 48 h	Redner and Stickney (1979)
B. SALTWATER			
Diplodus sargus (larvae)	0.36	Static, 24 h	Brownell (1980)
Gaidropsarus capnesis (larvae)	0.46	Static, 24 h	Brownell (1980)
Lithognathus mormyrus (larvae)	0.38	Static, 24 h	Brownell (1980)

(continued)

Table 2-2. Continued

Organism	LC_{50} (mg/L)	Exposure conditions	Reference
B. SALTWATER (continued)			
Oncorhynchus tschawytscha (Chinook salmon parr)	0.87-1.=2.19	Flowthrough, 24 h Variable salinity 5.2-9.6‰	Harader and Allen (1983)
Pachymetopon blochii (larvae)	0.42	Static, 24 h	Brownell (1980)
Salmo salar (Atlanta salmon 2-year smolt)	0.08-0.20	Static, 24 h Variable salinity 5.7-9.6‰	Alabaster et al. (1983)
Sciaenops ocellatus (Red drum post hatch larvae)	0.39	Static 96 h	Holt and Arnold (1983)

production. Necrosis and frost injury may occur from ammonia saturation of membrane lipids (Van Haut and Prinz, 1979; Van der Eerden, 1982).

Table 2-3. Acute Lethal Concentration Values for Unionized Ammonia in Aquatic Invertebrates

Organism	LC_{50} (mg/L)	Exposure conditions
Asellus vaccvitzai *(Isopod adult)*	5.02	Flowthrough, 96 h
Callibaetis skokianus *(Mayfly nymph)*	3.09	Flowthrough, 96 h
Crangonyx pseudogracilis *(Amphipod adult)*	3.12	Flowthrough, 96 h
Helisoma trivolvis *(Snail adult)*	2.37	Flowthrough, 96 h
Musculium transversum *(Fingernail clam adult)*	1.10	Flowthrough, 96 h
Orconectes immunis *(Crayfish adult)*	18.3	Flowthrough, 96 h
Philartcus quaens *(Caddisfly larvae)*	10.1	Flowthrough, 96 h
Physa gyrina *(Snail adult)*	1.95	Flowthrough, 96 h
Simocephalus [illegible] *(Cladoceran)*	1.71	Flowthrough, 48 h

Source: Arthur et al. (1987)

3. Health Effects

3.1 Pharmacokinetics and Metabolism

The essential role of ammonia and nitrogen in amino acid, protein, and nucleic acid metabolism by living organisms has been extensively discussed in standard textbooks and monographs. This section summarizes the available information on the metabolism of exogenous ammonia by mammals. The metabolic activities leading to the production and elimination of endogenous ammonia, as well as the possible chemical reactions leading to ammonia toxicity are discussed in the section on biochemical effects.

Egle (1973) studied the uptake and retention of ammonia in both the upper and lower respiratory tract of dogs exposed to ammonia at concentrations ranging from 346 to 1,076 mg/m^3 (459 to 1,522 ppm). He found that ammonia retention in the lower respiratory tract was slightly less than that of the upper respiratory tract. Retention ranged from 79.8 to 84.0 percent but was not concentration-related. Ammonia retention by the respiratory tract of humans was reported by Landahl and Hermann (1950) and Silverman et al. (1949). When subjects were exposed to ammonia concentrations varying from 40 to 355 mg/m^3 (57 to 502 ppm), approximately 92 percent was retained in the lungs but without any concentration-related effect (Landahl and Hermann, 1950). Silverman et al. (1949) found that exposure of human subjects to ammonia vapors at 353 mg/m^3 (500 ppm) for a period of 30 minutes resulted in a steady increase in ammonia concentrations in exhaled air. At equilibrium, about 80 percent of the inhaled ammonia was released in expired air.

Schaerdel et al. (1983) studied the pulmonary absorption of ammonia gas by male rats by exposing the rats from 11 to 818 mg/m^3 (15 to 1,157 ppm) ammonia for 1 day. They found a significant increase in blood ammonia levels with an increase in the ammonia exposure level, but blood levels decreased with time, suggesting that the body in some way compensates for the increase in blood ammonia. There were no significant effects noted on pH, pCO_2, pO_2, liver cytochrome P-450 concentration, or ethylmorphine-N-demethylase activity. In another study, blood and brain ammonia levels, blood glutamate, glutamine, creatinine, and urea nitrogen levels, and alkaline phosphatase activity were not affected in male rats exposed to 3.1 ± 0.21, 0.35 ± 0.07, or 0.14 ± 0.21 mg/m^3 (4.4 ± 0.3, 0.5 ± 0.1, or 0.2 ± 0.3 ppm) of ammonia generated from decomposing urine and feces in animal rooms (White and Mans, 1984).

Cooper and Lai (1987) studied the metabolism *in vivo* of ammonia by rat brain. Male Wistar rats (normal, acutely hyperammonemic, or chronically hyperammonemic) were treated with ^{13}N-ammonia via a carotid artery cannula. In both normal and hyperammonemic rats, the major portion of the ^{13}N-ammonia nitrogen was present as the amide nitrogen of glutamine. The rate of conversion of blood-denied ammonia to glutamine was rapid in normal rats ($t_{1/2} \leq 3$ seconds only) and slower in hyperammonemic rats ($t_{1/2} \leq 10$ seconds only). Hyperammonemia did not induce increased glutamine synthetase activity in rat brain.

Manninen et al. (1988) exposed groups of five female Wistar rats 6 hours/day for 5, 10, or 15 days to each of the following ammonia concentrations in air: 0, 18, or 212 mg/m^3 (0, 25, or 300 ppm). On day 5 of exposure, a concentration-dependent increase in blood ammonia and an increase of blood and brain glutamine were observed in rats exposed at 212 mg/m^3 compared with controls. By day 10, blood ammonia and blood and brain glutamine levels were similar to those of controls.

The initial biochemical reactions involved in the incorporation of ammonia into organic molecules in mammals involve the following: (1) the biosynthesis of glutamic acid from ammonia and alpha-ketoglutarate; (2) the biosynthesis of glutamine; (3) the formation of carbamyl phosphate; (4) the biosynthesis of asparagine; and (5) some other relatively rare processes. However, it appears that the route of administration drastically alters the distribution of ammonia ($^{15}NH_4^+$) between alpha-amino, amidine, and amide nitrogen of organ proteins. Vitti et al. (1964) found that when ^{15}N-ammonium citrate was given intragastrically or intraperitoneally to untreated and growth-hormone-treated hypophysectomized female Sprague-Dawley rats, extensive labeling of alanine, arginine, glutamic acid, and other amino acids of liver protein occurred. In contrast, subcutaneous injection resulted in extensive labeling of the amide nitrogen of glutamine. In addition, various levels of ^{15}N label were found in proteins of the heart, kidneys, and spleen, although the distribution varied among the various amino acids analyzed. The relative rate of incorporation of ^{15}N was highest in the liver and lowest in the heart and varied with the route of administration (subcutaneous > intraperitoneal > intragastric). The authors suggested that ammonia administered intragastrically or intraperitoneally was metabolized largely by pathways involving hepatic glutamic dehydrogenase and carbamyl synthetase, whereas subcutaneously administered ammonia is metabolized, to a great extent, by the glutamine synthetase route.

Following intravenous administration of ^{15}N-ammonia in male rats, ammonia was incorporated mainly into the amide position of glutamine (Duda and Handler, 1958). Approximately 90 percent of the isotope was incorporated into glutamine and urea 30 minutes after administration of 52.2 micromoles (mol) of ^{15}N-ammonia, with 80 percent being glutamine amide nitrogen. Urea synthesis represented a fixed percentage of available ammonia over a large concentration range. Incorporation into glutamine, urea, and glutamic acid reached a maximum at 20 minutes, but the specific activity of glutamine was approximately seven times that of either urea or glutamic acid. The distribution of labeled glutamine and urea in the tissues of rats following intravenous administration of 47.5 mol of ^{15}N-ammonium lactate was also determined by these investigators. The residue levels in glutamine and urea in various organs, expressed as µmol of glutamine and urea, respectively, were as follows: carcass (25.85, 5.60); liver (1.37, 0.39); heart (0.30, 0.03); kidneys (0.11, 0.15); spleen (0.10, 0.023); brain (0.08, 0.01); and testes (0.051, 0.028).

A fraction of exogenous ammonia is excreted via the lungs in expired air. Measurable amounts (about 269 g/m^3, 377 ppb) of free ammonia were found in the expired air of dogs injected intravenously with ammonium acetate (Robin et al., 1959). Exposure of human subjects to ammonia vapor at 353 mg/m^3 (494 ppm) for a period of 30 minutes also resulted in a steady increase in ammonia concentrations in exhaled air. At equilibrium, about 80 percent of the inhaled ammonia was released in expired air (Silverman et al., 1949).

Like exogenous ammonia, endogenous ammonia is also excreted via the lungs in expired air. For instance, Barrow and Steinhagen (1980) found endogenous ammonia in the expired air of rats at concentrations ranging from

7 to 250 µg/m^3 (10 to 353 ppb) in nose-breathing animals and 24 to 526 µg/m^3 (34 to 744 ppb) in tracheal-cannulated animals. They attributed these differences to the absorptive effect of moisture in the respiratory tract of nose breathers.

Ammonia is also excreted in the urine as urea. A study by Minana et al. (1988) indicated that in groups of 18 male Wistar rats given a diet containing 20 percent (w/v) ammonium acetate for 15 days and then a single intraperitoneal injection of 7 mmol ammonium acetate/kg, ammonia was initially sequestered and finally eliminated in the urine as urea. Saul and Archer (1984) also showed that repeated oral administration of ^{15}N-ammonium chloride to male Sprague-Dawley rats resulted in low but significant amounts of excess ^{15}N-nitrate in the urine. Rats were gavaged with 1,000 µmol of ^{15}N-ammonium chloride daily for 5 days. Nitrate was detected in the urine during the exposure period and on 5 subsequent days; approximately 0.008 percent of the dose was converted to nitrate. The authors suggested that hydroxylamine was a possible intermediate in the ammonia oxidation process, and postulated that ammonia is oxidized *in vivo* by a nonenzymatic process that involves active oxygen species such as the hydroxyl radical. Similar results were reported by Wagner et al. (1985) after continuous intravenous infusion of $^{15}NH_3$ to male Sprague-Dawley rats over a 96-hour period.

3.2 Biochemical Effects

Ammonia is a key metabolite in mammals and plays an essential biochemical role in acid-base regulation and in the biosynthesis of purines, pyrimidines, and nonessential amino acids (Kvamme, 1983; Visek, 1984; Stryer, 1981). A high concentration of endogenous ammonia, however, is quite toxic to mammals and may lead to life-threatening conditions.

The gastrointestinal (GI) tract is a major site of ammonia production. Amino acid deaminases and ureases of bacterial flora in the colon liberate ammonia from dietary amino acids and urea. Newly generated ammonia is transported to the liver through the portal circulation, where it is converted to urea. The urea is then transported by the blood to the kidneys for excretion:

$$\alpha\text{-ketoglutarate} + NH_3 + NADH + H^+ \rightleftharpoons \text{glutamate} + NAD^+ + H_2O$$

$$NH_3 + CO_2 + 2ATP + H_2O \rightleftharpoons \text{carbamoylphosphate} + 2ADP + Pi$$

$$\text{Carbamoylphosphate} \rightleftharpoons \text{urea}$$

The kidneys produce ammonia from the deamination of glutamine (Good and DuBose, 1987; Dass and Welbourne, 1986; Eriksson et al., 1985; Windmueller and Spaeth, 1978; Visek, 1984). The ammonia produced by the kidneys acts as an urinary buffer (Windmueller and Spaeth, 1978). The metabolic activity of skeletal muscle also generates ammonia (Eriksson et al., 1985). In the central nervous system, the purine nucleotide cycle appears to be the main generator of ammonia, which under normal conditions is incorporated into glutamine (Kvamme, 1983).

$$NH_3 + \alpha\text{-ketoglutarate} + NADH + H^+ \rightleftharpoons \text{glutamate} + NAD^+ + H_2O$$

$$ATP + \text{glutamate} + NH_3 \rightleftharpoons \text{glutamine} + ADP + Pi$$

The liver is the only organ that has a complete urea cycle that converts ammonia to urea. In other organs, ammonia is incorporated into glutamine. Muscle tissue comprises the largest glutamine pool in humans (Lund, 1980; Windmueller and Spaeth, 1978).

The importance of the urea cycle is not restricted to detoxifying ammonia; it also exchanges substrates with the citric acid cycle and provides substrates for the synthesis of pyrimidines and polyamines that regulate RNA and protein synthesis. For this reason, deficient or abnormal operation of the urea cycle may have serious metabolic consequences (Grisolia et al., 1976).

In humans, excretory mechanisms for detoxification and removal of ammonia are very rapid. For instance, under normal conditions, the hepatic portal circulation assures that all of the ammonia from the GI tract is transported to the liver for detoxification. Fifty percent of the arterial blood ammonia is detoxified by the skeletal muscle in healthy individuals (Freed and Gelbard, 1982; Lockwood et al., 1979). At the same time, the urea cycle normally operates at about 60 percent capacity (Hems et al., 1966), thus it is the availability of the substrate that may limit the rate of urea production. Fico et al. (1986) studied the rate of urea synthesis in human liver samples obtained by biopsy. They found that increasing the ammonia concentration in the incubation medium from 0 to 5.0 mM produced a 200 percent increase in urea synthesis.

Inherited conditions in children have been reported in which all or some of the enzymes participating in the urea cycle were defective (Hjelm et al., 1986; Brusilow, 1985; Shambaugh, 1978; Zimmermann et al., 1985). Such subjects exhibited various neurologic disorders, hyperammonemia, inhibited growth, and protein intolerance. Several acquired diseases can also affect the urea cycle enzymes (Zimmerman et al., 1985; Glasglow, 1983; Boutros et al., 1980), causing severe hyperammonemia, hyperaminoaciduria (Hilty et al., 1974), hepatic failure, and encephalopathy. In pathologic conditions such as alcoholic hepatitis, uremia, and liver cirrhosis, defective urea-cycle enzymes are also present (Müting et al., 1986; Swendseid et al., 1975; Maier et al., 1974; Brown et al., 1967).

It is possible that exogenous ammonia may cause a potential health risk under certain conditions to man (e.g., genetic or metabolic disorder). However, since ammonia is severely irritating to sensitive areas such as the eyes, skin, lungs, and throat, it is likely that humans will avoid exposure to quantities of "environmental" ammonia that can produce metabolic toxicity.

Acute exposure of mice for 2 days to ammonia vapors (50,000 ppm) increased the activity of sodium ion (Na^+) and potassium ion (K^+)-activated ATPase of the brain, resulting in an increased concentration of adenine derivatives (Sadasivudu et al., 1979, 1977), and decreased the activity of adenosine deaminase, thus reducing the degradation of adenosine (Sadasivudu et al., 1981). Since adenosine has been implicated both as a cerebral depressant as well as a sleep-inducing agent (Haulica et al., 1973), its accumulation could be a major factor in the depression of brain function. Alternatively, a rise in ATPase activity may lead to stabilization of neuronal membranes and increased transport of NH_4^+ into glial cells, exceeding the detoxifying ability of the cells. Increased transport of NH_4^+ into glial cells may possibly be due to its similarity to hydrated K^+, whose concentration is normally maintained by these cells (Lewis, 1976). Hence, this could produce a gross disturbance in ionic fluxes possibly leading to depression of neuronal transmission, the degree of which would depend on the extent of damage to the glial cells (Sadasivudu et al., 1979).

Chronic exposure to 50,000 ppm ammonia also alters the metabolism of amino acids belonging to the glutamic acid family (gamma-aminobutyric acid, alanine, glutamic acid, aspartic acid, glutamine) by increasing the activities of aspartate aminotransferase, glutamate dehydrogenase, and glutamine synthetase. This change facilitates greater removal of ammonia ultimately in the form of glutamine, thus compensating for a rise in the level of ammonia (Sadasivudu et al., 1979). The process occurs in the astroglial cells, which are known to possess most of glutamine synthetase activity in the brain (Martinez-Hernandez et al., 1977).

Hepatic encephalopathy has been linked with a derangement in the metabolism of a number of neurotransmitters like catecholamines, serotonin, gamma-aminobutyric acid (GABA), and acetylcholine (Fischer and Baldessarini, 1976; Biebuyck et al., 1975; Walker et al., 1971). Increased ATPase and decreased monoamine oxidase (MAO) and glutamate decarboxylase (GD) activities in all three regions of the brain were observed in mice intraperitoneally injected with 200 mg/kg ammonium chloride (Sadasivudu and Murthy, 1978). Glutamate decarboxylase (GD) and GABA-aminotransferase (GABA-T) are involved in the production and metabolism of GABA, whereas MAO degrades catecholamines and serotonin. While an increase in ATPase activity leads to membrane stabilization, GABA is known to bring about hyperpolarization (Krnjevic et al., 1966). Decreased GD and GABA-T activities may be regarded as compensatory because they reduce the GABA level. A decrease in MAO activity would tend to raise the levels of catecholamines and serotonin. An increase in catecholamine concentration, in particular, would promote consciousness in the animal. However, following exposure to 50,000 ppm ammonia vapors for 2 and 5 days, increased MAO levels in the cerebellum were observed. A greater destruction of biogenic amines may lead to a state of unconsciousness (Sadasivudu and Murthy, 1978).

During the last three decades, several mechanisms have been proposed to explain the biochemical basis for ammonia neurotoxicity. Because the brain is highly vulnerable to decreases in the ATP level, these hypotheses postulate an eventual decrease in available cerebral energy due either to reduced production or enhanced utilization of ATP during ammonia detoxification and/or due to ammonia-induced stimulation of ATPase activity (McCandles and Schenker, 1981; Walker and Schenker, 1970). Other theories include the formation or accumulation of GABA, an inhibitory neurotransmitter (Goetcheus and Webster, 1965), and depletion of acetylcholine (Braganca et al., 1953). However, none of these hypotheses has been conclusively proven. It is possible that ammonia intoxication produces a multiplicity of biochemical injuries. The following theories are briefly discussed.

McKhann and Tower (1961) suggested that ammonia reduces the incorporation of pyruvate into the tricarboxylic acid (TCA) cycle, thus slowing the oxidative metabolism. This conclusion was drawn from an *in vitro* observation that high concentrations of ammonium chloride (15 mM) inhibit oxygen consumption in cat cortex mitochondria, indicating impaired pyruvate decarboxylation. However, tests conducted on the brain of ammonia-intoxicated rats and from brains incubated with ammonium chloride or ammonium acetate (2 to 18 mM) failed to reveal any alteration in pyruvate decarboxylation (Walker and Schenker, 1970; Ratnakumari et al., 1986).

Based on *in vitro* studies with high ammonia concentrations, Worcel and Erecinska (1962) suggested that cerebral detoxification of ammonia to glutamate depletes the NADH pool, resulting in decreased amounts of NADH available for ATP formation in the mitochondria. However, results from *in vivo*

studies indicated that the cerebral cytoplasmic NADH:NAD$^+$ ratios increased during acute ammonia intoxication due to a marked increase in the lactate:pyruvate ratio (Hawkins et al., 1973; Hindfelt, 1973). Moreover, there was an apparent decrease in NADH:NAD$^+$ ratio in the mitochondria, suggesting a failure to transport reduced equivalents from the cytoplasm to the mitochondria (Hindfelt et al., 1977).

The "Energy Depletion Hypothesis" was suggested by Bessman and Bessman (1955). According to this hypothesis, ammonia entering the brain reacts with alpha-ketoglutarate (alpha-KG) and NADH, forming glutamate. Glutamate would deplete the TCA cycle of one of its dicarboxylic acids, resulting in a drop in the cerebral oxygen utilization observed in hepatic coma. This reduction in oxidative metabolism would also result in a drop in ATP formation in the brain, eventually leading to coma. It has been observed that the brains of hepatic coma patients often exhibit ammonia uptake (Bessman and Bessman, 1955) and decreased oxygen consumption (Fazekas et al., 1956). Further, after ammonia injections, the concentrations of alpha-KG were decreased in the cerebral cortex and whole brain of dogs and mice, respectively (Bessman, 1961; Clark and Eiseman, 1958). However, other studies with animals have failed to detect any significant change in the concentrations of alpha-KG or ATP in the brain during the induced ammonia intoxication (Ratnakumari et al., 1986; Raabe and Lin, 1984; Hawkins et al., 1973; Hindfelt and Siesjö, 1970, 1971). Bessman and Pal (1982) suggested that the major problem with the acceptance of this hypothesis in the past was the lack of exact correlation between levels of ammonia concentration in the blood and the mental state of the patient. In fact, correlation between cerebral symptoms and CSF glutamine content was somewhat better than the correlation with ammonia concentration. However, they have now demonstrated the presence of a relation between ammonia concentration in the blood and the state of consciousness.

Another theory explains the depletion of cerebral ATP through enhanced synthesis of glutamine (Nakazawa and Quastel, 1968). A fourfold increase in cerebral glutamine was found within 15 minutes after administration of an acute dose of ammonium acetate to rats (du Ruisseau et al., 1957). Other investigators have reported similar findings (Berl et al., 1968). However, it has been suggested that glutamine synthesis alone cannot utilize enough ATP to affect cerebral function, unless a "vital" ATP pool is involved (Bessman, 1961). Administration of methionine sulfoximine, a potent inhibitor of glutamine synthetase, caused a marked decrease in ammonia toxicity in mice. It was concluded that ammonia intoxication does not depend on the mere presence of high cerebral ammonia content, but is related to a metabolic process that occurs directly or indirectly through the major known pathway of cerebral ammonia detoxication, i.e., synthesis of glutamine (Warren and Schenker, 1964). Hindfelt (1973) failed to support the sparing mechanism of methionine sulfoximine through ATP-saving inhibition of glutamine synthesis. In addition, Hawkins et al. (1973) found no significant arteriovenous difference in glutamate or glutamine concentration in acutely intoxicated mice. Although a considerable amount of ammonia was incorporated into glutamine, it was not rapidly released from the brain into the circulatory system.

Hawkins et al. (1973) suggest that the general increase in nerve cell excitability and activity that results in convulsions, as well as the increased metabolic rate of the brain, may be due to Na^+ and K^+ stimulation of ATPase activity produced by ammonia. After an injection of ammonium acetate, the plasma K^+ concentration increased from 3.3 to 5.4 mol/L, with no significant increase in Na^+ concentration. A possible decrease of 15 mV in the resting

transmembrane potential was calculated. Accordingly, the likely mechanism for pharmacologic action of ammonia is the effect on the electric properties of nerve cells. Extracellular ammonia-like K^+ decreases the resting transmembrane potential, and, therefore, the resting potential is closer to the threshold for nerve conduction. This could then cause a general increase in nerve-cell excitability leading to convulsions.

Ulshafer (1958) suggested that the depletion of ATP may cause a decrease in cerebral acetylcholine, which requires ATP for its synthesis. Administration of sufficient ammonium carbonate to produce convulsions in rats caused a decrease in the brain content of acetylcholine. Ammonia also inhibits the synthesis of acetylcholine in brain cortex slices, which can be relieved by the addition of glutamine synthetase inhibitors (Braganca et al., 1953). However, Walker et al. (1971) failed to detect any change in acetylcholine, serotonin, or norepinephrine during the development of acute ammonia-induced coma.

Raabe and Lin (1983,1984) found that systemic ammonia toxicity inactivates the extrusion of the chloride ion (Cl^-) from the neurons and thus decreases the hyperpolarizing action of postsynaptic inhibition, producing the first signs of ammonia neurotoxicity. The decrease in the hyperpolarizing action of postsynaptic inhibition was without a concurrent decrease in energy metabolism (decrease of pyruvate, α-ketoglutarate, glutamate, or ATP) as had been suggested by Bessman and Bessman (1955). Similar results were also reported by Iles and Jack (1980).

3.3 Acute Toxicity

Several studies have been conducted with laboratory animals to determine the effects of acute exposure to ammonia. Acute toxicity values, presented in Table 3-1, suggest that ammonia is very toxic at high exposure levels.

In animals, compound- and concentration-related effects resulting from exposure to ammonia progress from mild irritation of the respiratory system and mucous membranes to convulsions, acute pulmonary edema, coma, and death. Typical signs of toxicity associated with exposure to ammonia include initial excitation, closed eyes, labored respiration, mouth breathing, nose pawing, scratching, ocular and nasal discharge, and coughing (Kapeghian et al., 1982; Silver and McGrath, 1948; Appelman et al., 1982; Boyd et al., 1944; Weedon et al., 1940; Dodd and Gross, 1980; Cralley, 1942; Dalhamn, 1956; Dalhamn and Sjoholm, 1963; Drummond et al., 1978).

Exposure to sublethal and lethal concentrations of ammonia has produced adverse effects in the respiratory tract and liver in some species. Kapeghian et al. (1982) studied the effect of inhalation of ammonia gas in mice exposed to ammonia levels ranging from 0 to 3,436 mg/m^3 (0 to 4,860 ppm) for 1 hour followed by an observation period of 14 days. Exposed animals exhibited irritant effects (excitation, rapid, vigorous tail revolutions, eye blinking, nose scratching, and dyspnea) immediately following exposure. At exposure levels of 2,793, 2,964, 3,188, and 3,450 mg/m^3 (3,950, 4,220, 4,490, and 4,860 ppm) there was 25, 42, 67, and 100 percent mortality, respectively. Diffusely hemorrhagic lungs were noted in animals that died during exposure. No deaths were noted at exposure levels lower than 2,792 mg/m^3. Appelman et al. (1982) found that exposure to ammonia levels ranging from 21,353 to 38,547 mg/m^3 (30,075 to 54,292 ppm) for 10 minutes; 18,642 to 23,641 mg/m^3 (26,256 to 33,305 ppm) for 20 minutes; 12,862 to 17,164 mg/m^3 (18,116 to 24,175 ppm) for 40 minutes, and 10,059 to 13,491 mg/m^3 (14,169 to 19,002

Table 3-1. Acute Toxicity Values for Ammonia in Laboratory Animals

Route/species, sex	Acute toxicity value	Exposure duration, min	Reference
Inhalation			
Mouse, M	LC_{50} = 2,991 mg/m^3 (4,230 ppm)	60	Kapeghian et al. (1982)
Mouse	LC_{50} = 6,988 mg/m^3 (9,884 ppm)	10	Silver and McGrath (1948)
Rat, M	LC_{50} = 26,327 mg/m^3 (37,238 ppm)	10	Appelman et al. (1982)
Rat, F	LC_{50} = 31,899 mg/m^3 (45,119 ppm)	10	Appelman et al. (1982)
Rat, M	LC_{50} = 9,997 mg/m^3 (14,140 ppm)	60	Appelman et al. (1982)
Rat, F	LC_{50} = 13,977 mg/m^3 (19,770 ppm)	60	Appelman et al. (1982)
Cat	LC_{50} = 7,127 mg/m^3 (10,080 ppm)	60	Boyd et al. (1944)
Rabbit	LC_{50} = 7,127 mg/m^3 (10,080 ppm)	60	Boyd et al. (1944)
Oral			
Guinea pig[a]	LD_{75} = 900-1,200 mg/kg	NA[b]	Koenig and Koenig (1949)
Intravenous			
Chicken	LD_{50} = 46.3 mg/kg	NA	Wilson et al. (1968)
Mouse	LD_{50} = 95.9 mg/kg	NA	Wilson et al. (1968)
Intraperitoneal			
Rat[a]	LD_{100} = 400 mg/kg	NA	Koenig and Koenig (1949)
Chicken[c]	LD_{50} = 177.5 mg/kg	NA	Wilson et al. (1968)
Mouse[c]	LD_{50} = 184.3 mg/kg	NA	Wilson et al. (1968)

[a]Ammonium chloride used.
[b]NA = Not applicable.
[c]Ammonium acetate used.

ppm) for 60 minutes produced excitability and nasal and eye irritation in rats. Macroscopic examination revealed hemorrhagic lungs in all exposed animals. Exposure-related deaths occurred in all exposure groups except those animals exposed to 21,353 mg/m^3 ammonia for 10 minutes. Exposure to ammonia gas levels of 6,063 to 8,946 mg/m^3 (8,540 to 12,600 ppm) for 10 minutes resulted in 25 to 80 percent mortality. Of 180 mice tested, 100 died within the 10 minute exposure period (Silver and McGrath, 1948). An increase in the hexobarbital sleeping time was reported by Kapeghian et al. (1985) after exposing mice to 3,110 mg/m^3 (4,380 ppm) ammonia for 4 hours; however, this exposure level was lethal to 4 of the 12 animals. No effect was noted on the hexobarbital-induced sleeping time in animals exposed to 958 mg/m^3 (1,350 ppm) ammonia for 4 hours; however, the latent periods were significantly reduced in both exposure groups.

The results of acute exposure to lower levels of ammonia are conflicting. Schaerdal et al. (1983) saw no signs of irritancy or histological changes in the

respiratory tract of rats exposed to ammonia levels of 11 to 818 mg/m^3 (15 to 1,157 ppm) for 1 day or 3 to 507 mg/m^3 (4 to 714 ppm) for 3 or 7 days. The National Research Council (1977) reported no signs of ill effects in 4 mice and 7 rats exposed to 707 mg/m^3 (1,000 ppm) ammonia for 16 hours; however, 1 rat died during the exposure period. Gross examination revealed congestion, hemorrhage, and edema of the lungs. Slight irritation was reported in rats exposed to from 339 to 403 mg/m^3 (480 to 570 ppm) ammonia for 4 hours (Carson et al., 1981). Exposure to 71 to 212 mg/m^3 (110 and 300 ppm) ammonia for 6 hour intervals reduced free access wheel running in rats and mice. Reductions in wheel running during exposure to irritants may be interpreted to reflect sensory irritation (Tepper et al., 1985). Wood (1981) calculated the aversive concentration at which 50 percent (AC_{50}) of the ammonia exposures were terminated using an operant conditioning procedure. His calculations indicate that ammonia produces irritant effects in mice at levels < 243 mg/m^3 (344 ppm). In a later work, Tepper and Wood (1985) using a similar operant conditioning procedure, calculated an AC_{50} value for mice of 303 ± 92 mg/m^3 (428 ± 130 ppm). After repeated exposures to high levels of ozone prior to ammonia exposure, the AC_{50} value decreased from 303 to 165 mg/m^3 (428 to 233 ppm). Exposure to 198 mg/m^3 (280 ppm) ammonia for 36 hours resulted in frothing of the mouth and excessive secretions from the noses of pigs. After the exposure period, convulsions occurred and respiration was short and irregular (Stombaugh et al., 1969). Merilan (1973) saw a significant decrease in respiratory rates in calves exposed to 35 to 71 mg/m^3 (50 and 100 ppm) ammonia for 7.5 hours. Exposure to 35 to 71 mg/m^3 for 2.5 hours did not produce this effect (Mayan and Merilan, 1976). Vesell et al. (1973) reported that the ammonia produced from fecal matter in animal cages could produce hepatic microsomal enzyme inhibition (ethylmorphine N-demethylase and aniline hydroxylase activity) in rats. This finding was not confirmed by Schaerdal et al. (1983) and Kapeghian et al. (1985) after exposing rats to 505 mg/m^3 (714 ppm) ammonia for 7 days and mice to 248 mg/m^3 (350 ppm) ammonia for 4 days. Dodd and Gross (1980) detected necrosis and sloughing of the airway mucosal surface in cats exposed to 707 mg/m^3 (1,000 ppm) ammonia for 10 minutes. A cessation of tracheal ciliary activity was seen in rats 7 to 8 minutes after exposure to 2 mg/m^3 (3 ppm) ammonia, 150 seconds after exposure to 4 to 5 mg/m^3 (6 to 7 ppm), 20 seconds after exposure to 14 mg/m^3 (20 ppm), 10 seconds after exposure to 32 mg/m^3 (45 ppm), and 5 seconds after exposure to 64 mg/m^3 (90 ppm) (Dalhamn, 1956). A reduction in ability to clear pulmonary bacteria (schence in cats exposed to 707 mg/m^3 (1,000 ppm) ammonia for 10 minutes. A cessation of tracheal ciliary activity was seen in rats 7 to 8 minutes after exposure to 2 mg/m^3 (3 ppm) ammonia, 150 seconds after exposure to 4 to 5 mg/m^3 (6 to 7 ppm), 20 seconds after exposure to 14 mg/m^3 (20 ppm), 10 seconds after exposure to 32 mg/m^3 (45 ppm), and 5 seconds after exposure to 64 mg/m^3 (90 ppm) (Dalhamn, 1956). A reduction in ability to clear pulmonary bacteria (*Escherichia coli*) was found in pigs exposed to 35 to 53 mg/m^3 (50 to 75 ppm) ammonia for 2 hours (Drummond et al., 1978). While ammonia had little effect on performance or respiratory tract structure, the authors suggested that exposure to ammonia could be a contributing factor in pulmonary tract infection.

Buckley et al. (1984) exposed via inhalation groups of 16 to 24 male Swiss-Webster mice to ammonia at the RD_{50} concentration of 214 mg/m^3 (303 ppm) 6 hours/day, for 5 days. An evaluation of the ammonia-induced histopathological lesions of the respiratory tract indicated mild to moderate epithelial exfoliation, erosion, ulceration, necrosis, inflammation, and squamous

metaplasia in the nasal cavity. No lesions were observed in the olfactory epithelium.

Rothenberg et al. (1986) exposed five male and three female beagle dogs (nose only) to 1 mg/m^3 ammonium sulfite mixed with sulfate for 1 hour. The levels of sulfur dioxide and ammonia were < 0.5 ppm and < 5.0 ppm, respectively. No statistically significant differences were observed in the tracheal mucosal clearance rate between preexposure and postexposure. In a separate experiment, inhalation exposure (nose only) of 12 male and 12 female guinea pigs to aerosol concentrations of 50, 250, or 450 mg/m^3 of ammonium sulfite (60 to 80 percent) for 1 hour produced no deaths at any level.

Minana et al. (1988) investigated the protective effect of long-term ammonium ingestion against acute ammonium intoxication in hyperammonemic rats. Groups of 18 male Wistar rats were fed either a control diet or a diet containing 20 percent (w/v) ammonium acetate for 15 days. Both the control and the treated rats were then given a single intraperitoneal injection of 7 mmol ammonium acetate/kg. Blood ammonia, blood urea, and glutamine levels were determined at various intervals (1 to 8 hours postinjection). Survival was higher (nine survivors) for hyperammonemic rats than for control rats (one survivor). In addition, of the nonsurvivors, hyperammonemic rats died within 31 ± 10 minutes, and the control rats died within 18 ± 5 minutes postexposure. Ingestion of ammonium-containing diet for 15 days had a protective effect against a single high dose of ammonia. Blood ammonia levels were the same (2 mM) for both groups; the maximum was reached after 15 and 30 minutes for hyperammonemic and control rats, respectively, suggesting a more rapid detoxification in hyperammonemic rats.

3.4 Subchronic Toxicity

Subchronic exposure to ammonia levels higher than those encountered in ambient air produces adverse effects on the tissues of the respiratory tract and impairs the pulmonary defense system. It may also produce anorexia, increase the tendency towards, or severity of, respiratory tract infections, and/or produce degenerative changes in the lungs, liver, kidneys, and spleen.

Coon et al. (1970) in four experiments studied the effects of repeated or continuous exposure to varying concentrations of ammonia gas in several species. Table 3-2 gives the results of those experiments. In summary, nasal and ocular effects were associated with repeated exposure to ammonia at 778 mg/m^3 (1,100 ppm) in dogs and rabbits; however, these signs disappeared during the second week of exposure. No clinically significant effects were detected in guinea pigs, rabbits, dogs, and monkeys continuously exposed to ammonia at a concentration of 40 mg/m^3 (57 ppm) for 114 days. There were inflammatory changes noted in the lungs and kidneys of rats exposed to 127 mg/m^3 (181 ppm) ammonia continuously for 90 days. However, these changes were reported in 50 percent of the control and exposed animals. In rats exposed to 262 mg/m^3 (374 ppm) ammonia there were nonspecific circulatory and degenerative changes in the lungs and kidneys that, according to the authors, were difficult to specifically relate to ammonia exposure. Deaths occurred at concentrations of 460 and 455 mg/m^3 (650 and 672 ppm).

Numerous other subchronic toxicity studies have also been reported. Weatherby (1952) found that exposure of male guinea pigs to 120 mg/m^3 (170 ppm) (range 99 to 141 mg/m^3; 140 to 200 ppm) ammonia for 6 hours/day, 5 days/week for up to 18 weeks resulted in congestion of the spleen, liver, and kidneys and early degenerative changes in the suprarenal gland. No

Table 3-2. Results of Subchronic Exposures to Ammonia Gas in Several Species

Species	Exposure Level Duration	Results
Long-Evans-derived and Sprague-Dawley rats, Princeton-derived guinea pigs, New Zealand albino rabbits, male squirrel monkeys, purebred male beagle dogs	222 or 1,110 ppm (155 or 770 mg m^3) 8 hours day, 5 days week (30 exposures)	No mortality. Focal pneumonitis was noted in the lungs of one monkey at the 222-ppm exposure level. At 1,100 ppm, nasal and ocular irritation was noted in the dogs and rabbits; however, these signs disappeared during the second week of exposure. Nonspecific inflammatory changes were noted in the lungs of rats and guinea pigs.
Long-Evans-derived and Sprague-Dawley rats, Princeton-derived guinea pigs, New Zealand albino rabbits, squirrel monkeys, male beagle dogs	57 ppm (40 mg m^3) continuously for 114 days	No mortality or visible signs of toxicity. Lipid-filled macrophages were noted in the lungs of the dogs, one monkey, and one rat.
Long-Evans-derived and Sprague-Dawley rats	181 or 374 ppm (127 or 262 mg m^3) continuously for 90 days	No mortality. Inflammatory changes noted in the lungs and kidneys in 50 percent of the controls and animals exposed at 181 ppm. Twenty-five percent of the animals in the 374-ppm exposure group had mild nasal discharge. Nonspecific circulatory and degenerative changes in the lungs and kidneys were also noted in the animals exposed at 374 ppm.
Long-Evans-derived and Sprague-Dawley rats	650 ppm (455 mg m^3) continuously for 114 days	Experiment terminated on day 65 due to high mortality. Signs of dyspnea and nasal irritation noted in all exposed animals.

Source: Coon et al. (1970)

Table 3-2. Results of Subchronic Exposures to Ammonia Gas in Several Species

Species	Exposure Level Duration	Results
Long-Evans-derived and Sprague-Dawley rats, Princeton-derived guinea pigs, New Zealand albino rabbits, squirrel monkeys, male beagle dogs	672 ppm (470 mg/m^3) continuously for 114 days	High mortality in rats. Marked eye irritation in dogs and rabbits. Erythema, discharge, and opacity of the corneas of the rabbits. Heavy lacrimation and nasal discharge in the dogs. Consistent lung involvement in all exposed animals. In several animals of each species, fatty changes in liver plate cells, myocardial fibrosis, calcification of the renal tubular and bronchial epithelia, and proliferation of the renal tubular epithelium were detected. Similar but less severe findings were noted in controls.

Source: Coon et al. (1970)

significant effects were detected following exposure of guinea pigs and mice to an ammonia concentration of 14 mg/m^3 (20 ppm) for 28 days. When the exposure duration was increased to 42 days or when the ammonia concentration was increased to 35 mg/m^3 for guinea pigs, pulmonary edema, congestion, and hemorrhage were seen in both species (Anderson et al., 1964). Richard et al. (1978) found nasal irritation and severe inflammatory lesions in rats exposed to 353 mg/m^3 ammonia for 3 weeks which were not present after 8 weeks of exposure. The authors believed this finding suggested the occurrence of an adaptive process. Mayan and Merilan (1972) found no pathologic changes in the liver, lungs, spleen, or kidneys after exposing female white rabbits to 35 mg/m^3 ammonia for 2.5 to 3 hours (22 exposures) or 71 mg/m^3 for 16 exposures (duration of each exposure not indicated). Examination of guinea pig alveolar macrophages after subcutaneous inoculation with *Mycobacterium bovis* BCG and intradermal injection of 2.5 g of tuberculin-purified protein derivative (PPD) and exposure to 35 or 64 mg/m^3 (50 or 90 ppm) ammonia for 3 weeks resulted in no significant alterations in bactericidal or phagocytic activities. However, the addition of ammonia to cultures of alveolar macrophages from normal animals significantly inhibited the bactericidal activity of those cells (Targowski et al., 1984). An increase in the severity of rhinitis, otitis media, tracheitis, and pneumonia was seen by Broderson et al. (1976) after inoculating rats with *Mycoplasma pulmonis* and exposing them for 4 to 6 weeks to ammonia levels routinely found in animal cages 18 to 177 mg/m^3 (25 to 250 ppm). The authors also found pathologic changes in the nasal passages of animals exposed to 106 mg/m^3 (150 ppm) ammonia for 75 days and 177 mg/m^3 for 35 days. Schoeb et al. (1982) found that ammonia had a direct growth-promoting effect on *Mycoplasma pulmonis* which was responsible for respiratory disease syndromes in rats.

In commercial animal species, Deaton et al. (1982, 1984) showed that exposure of laying hens to ammonia at a concentration of 141 mg/m^3 (200 ppm) for 17 days resulted in a significant reduction in egg production. Deaton et al. (1982), Oyetunde et al. (1978), and Reece et al. (1981) found that exposure of chickens to sublethal concentrations of ammonia (18 to 141 mg/m^3) for up to 28 days significantly reduced body weight gain. Mild to moderate macroscopic and microscopic changes in the lungs and air sac were seen in chickens exposed to 71 mg/m^3 (100 ppm) ammonia for 4 weeks (Oyetunde et al., 1978). No significant effects were detected following the exposure of chickens to ammonia at a concentration of 14 mg/m^3 (20 ppm) for up to 28 days and turkeys for up to 6 days; however, pulmonary edema, congestion, and hemorrhage were detected in chickens exposed at 141 mg/m^3 for 17 to 21 days or 707 mg/m^3 (990 ppm) for 14 days, and in turkeys exposed at 35 mg/m^3 for 10 to 14 days. Also, chickens maintained in environments containing 14 mg/m^3 ammonia for 72 hours or 35 mg/m^3 (50 ppm) for 48 hours were found to be more susceptible to Newcastle disease virus (Anderson et al., 1964). Like Dalhamn (1956), Nagaraja et al. (1983) found that exposure to ammonia produced a reduction in tracheal ciliary activity. After exposure to 7 to 28 mg/m^3 (10 to 40 ppm) ammonia for 1 to 7 weeks, turkeys exhibited deterioration of the mucociliary apparatus which is thought to reflect a breakdown in the defense mechanism of the respiratory tract against an accumulation of pathogenic bacteria and viruses. With the exception of mild conjunctivitis and blepharitis in one pig, Curtis et al. (1975), found no evidence of structural aberrations in any organ or tissue of pigs exposed to ammonia levels of 35 to 53 mg/m^3 for up to 75 days. The National Research Council (1977) reported an increased thickness of tracheal

epithelium and goblet cells in pigs after exposure to 75 mg/m^3 (106 ppm) ammonia for 2 weeks.

3.5 Chronic Toxicity

No adequate information was found on the effects of chronic exposure to ammonia in animals.

3.6 Carcinogenicity

No information was found on the carcinogenic potential of inhaled ammonia in animals. However, oral administration of ammonium hydroxide and ammonia was not carcinogenic in mice. Toth (1972) investigated the carcinogenic potential of ammonium hydroxide in Swiss and C3H mice. Ammonium hydroxide was administered daily in the drinking water of Swiss mice at levels of 0.1, 0.2, or 0.3 percent (1,000, 2,000, or 3,000 ppm) and to C3H mice at a level of 0.1 percent over the normal life span of the animals. Ammonium hydroxide was not carcinogenic in either species, and did not affect the development of breast adenomas in C3H females. The incidences of breast adenomas in the treated and control groups were 60 and 76 percent, respectively. In another study, no significant increase in lung tumors was found in mice with a high sensitivity to lung tumorigenesis after the administration of 42 mg/kg ammonia twice a week by stomach tubes for 4 weeks (Uzvölgyi and Bojan, 1980).

3.7 Mutagenicity

Limited data suggest that ammonia may be mutagenic. Demerec et al. (1951) tested ammonia for its ability to induce back-mutations from streptomycin dependence (Sd-4) to nondependence in *Escherichia coli*. Bacterial suspensions were added to ammonia solutions ranging from 0.025 to 0.500 percent (250 to 5,000 ppm) in distilled water, and incubated at 37°C for 3 hours. Control cultures were incubated in distilled water only. A definite mutagenic activity was observed at concentrations of 0.25 and 0.50 percent (2,500 and 5,000 ppm); however, the proportion of survivors was lower than 2 percent.

Lubashev and Smirnov (1934) reported that 95 percent mortality occurred in larvae of *Drosophila melanogaster* (100-120 hr old) exposed to the fumes of 1 percent (10,000 ppm) ammonium hydroxide solutions. The offspring of the survivors showed a mutation rate of 0.54 percent while control cultures showed only 0.05 percent, which was a statistically significant effect.

Visek et al. (1972) examined the effect of ammonia in cultures of normal and transformed 3T3 cells. Normal 3T3 and SV-40 transformed 3T3 mouse fibroblasts were cultured in media with serum and antibiotics plus ammonia added as ammonium chloride. The amount of ammonia added was 0, 10, 20, or 35 µg/mL (0, 10, 20 or 35 ppm) of culturing medium. Normal morphology and cell multiplications were seen in both cell lines when ammonia was not added. However, when ammonia was added both cell lines showed distinct changes in the morphology and highly significant ($p < 0.001$) reductions in cell multiplications. These changes increased progressively as the concentration of ammonia increased. Control 3T3 cultures released significantly ($p < 0.001$) greater quantities of ammonia per cell than control cultures of transformed cells, but their multiplication was more adversely affected with the addition of

ammonia. The affect of ammonia on cell multiplication was independent of the pH of the medium.

3.8 Teratogenicity and Reproductive Effects

No information was found on the teratologic or reproductive effects of ammonia in animals.

3.9 Neurotoxicity

Elevated levels of ammonia in the blood of animals and humans have been known to cause neurologic disorders and encephalopathy. Hyperammonemia may result from liver failure or metabolic and genetic diseases that affect the synthesis of urea and/or removal of ammonia. The biochemical basis for ammonia neurotoxicity is discussed in Section 3.2.

3.10 Effects on Humans

Most of the available literature on the effects of ammonia on humans consisted of case reports following accidental exposure via inhalation; consequently, exposures were not well quantified. The major effects of acute exposure to ammonia are burns of the eyes, skin, and respiratory tract. Since ammonia is highly water soluble, these effects are likely the result of the formation of ammonium hydroxide *in situ*.

3.10.1 Ocular Toxicity

Eye injuries are the most common cause of permanent disability due to accidental acute exposure to ammonia (Helmers et al., 1971; Jarudi and Golden, 1973). Ammonia, in the form of ammonium hydroxide, forms soaps as it reacts with the fatty epithelial layer of the cornea, after which it traverses the stroma and disrupts the endothelium. Edema of the cornea can appear a few minutes after exposure. In a severe exposure, ammonia may reach the iris and start cataractous changes in the lens. The trabecular meshwork may become edematous and plugged with iris pigment and inflammatory cells. Following these changes, an increase in intraocular pressure can be detected a few hours after exposure. Weeks after exposure, infiltration of the cornea may result in fibrosis and neovascularization. Ulceration of the conjunctival surfaces may cause adhesion of the lids to the globe. The inflammatory progression may continue until the cornea, iris, and lens are fused into a mass of vascular granulation tissue.

Gaseous ammonia is slightly irritating to the human eye at a concentration of 99 mg/m^3 (140 ppm) and immediately irritating at 495 mg/m^3 (700 ppm) (National Research Council, 1977; Griffiths and Megson, 1984). Reported ocular effects following exposure to ammonia are inflamed eyes, lacrimation, swelling of the eyelids (O'Kane, 1983; Ward et al., 1983; Hoeffler et al., 1982; Close et al., 1980; Montague and Macneil, 1980; Ferguson et al., 1977; Verberk, 1977; Helmers et al., 1971; Silverman et al., 1949; Caplin, 1941), hyperemic conjunctiva (Hatton et al., 1979; Sobonya, 1977; Helmers et al., 1971; Levy et al., 1964; Caplin, 1941; Slot, 1938), and sustained corneal damage (Birken et al., 1981; Kass et al., 1972; Osmond and Tallents, 1968; Caplin, 1941). Highman (1969) described two cases in which ammonia was squirted in the face and eyes. The presenting signs mimicked those of acute angle closure glaucoma, i.e., oval, semidilated, nonreacting pupils, corneal edema, and a rapid rise in intraocular pressure (to 60 mmHg in the damaged

eye of one patient and 36 mmHg in the damaged eye of the other patient) (The normal range for intraocular pressure is 10 to 30 mmHg.) Continued medication was necessary to decrease and maintain intraocular pressure. Other signs observed in the two patients were burns of the eyelids, chemosis, and corneal ulcers.

Moeller (1974) examined ophthalmologic changes due to chronic exposure in 109 persons working in an ammonia plant. The average exposure time was 7.6 years. The following examinations were carried out: vision determination, slit lamp examination, ophthalmoscopy, examination of the central and peripheral visual fields, and anomaloscope examination. No ocular effects due to chronic ammonia exposure were noted.

3.10.2 *Respiratory Toxicity*

The range of odor threshold concentrations for ammonia in humans was reported to be from 0.5 to 35.0 mg/m^3 (0.7 to 50 ppm), with the average threshold concentration estimated at 4.0 mg/m^3 (5 ppm) (National Research Council, 1977). Many case report studies of accidental ammonia inhalation have classified the exposures as mild, moderate, or severe. Mild exposure usually results in temporary irritating respiratory symptoms; moderate exposure, in more insidious and prolonged effects; and severe exposure, in death and long-term irreversible respiratory changes. Close et al. (1980) reported that in moderately exposed persons, initial chest findings may be normal but may worsen with time due to insidious penetration of ammonia into the lower airways.

Immediate signs of accidental ammonia inhalation are dyspnea (Flury et al., 1983; O'Kane, 1983; Hoeffler et al., 1982; Close et al., 1980; Montague and Macneil, 1980; Dalton and Bricker, 1978; Sobonya, 1977; Walton, 1973; Kass et al., 1972; Levy et al., 1964; Caplin, 1941), wheezing, rhonchi, and rales (Flury et al., 1983; O'Kane, 1983; Montague and Macneil, 1980; Helmers et al., 1971; Sobonya, 1977; Levy et al., 1964; Caplin, 1941), chest pain (Montague and Macneil, 1980; Walton, 1973), nonproductive cough (O'Kane, 1983; Hoeffler et al., 1982; Montague and Macneil, 1980; Walton, 1973), productive cough (Price et al., 1983; Hoeffler et al., 1982; Caplin, 1941), nasal discharge and bronchial secretions (O'Kane, 1983; Helmers et al., 1971; Levy et al., 1964), acute upper airway obstruction (Close et al., 1980), aphonia (Montague and Macneil, 1980), laryngopharyngeal edema (Griffiths and Megson, 1984; Flury et al., 1983; O'Kane, 1983; Montague and Macneil, 1980; Dalton and Bricker, 1978; Osmond and Tallents, 1968; Levy et al., 1964), cyanosis (O'Kane, 1983; Dalton and Bricker, 1978; Walton, 1973; Caplin, 1941), hypoxemia and hypercapnia (Price et al., 1983; Flury et al., 1983; Hoeffler et al., 1982), decreased blood gas levels (O'Kane, 1983; Close et al., 1980; Montague and Macneil, 1980), pulmonary edema (Hoeffler et al., 1982; Chu, 1982; Griffiths and Megson, 1984; Birken et al., 1981; Sobonya, 1977; Helmers et al., 1971; Caplin, 1941), bronchospasm (O'Kane, 1983; Sobonya, 1977; Walton, 1973; Levy et al., 1964), and pseudomembranous covering of the pharynx wall (Flury et al., 1983).

Long-term effects of accidental ammonia inhalation are hypoxemia (Sobonya, 1977; Kass et al., 1972), pulmonary edema (Price et al., 1983; O'Kane, 1983), emphysema (Kass et al., 1972), bronchiectasis (Price et al., 1983; Kass et al., 1972), mucopurulent exudate arising from the tracheobronchial tree (Flury et al., 1983; Sobonya, 1977; Kass et al., 1972), infection with *Nocardia asteroides* (Sobonya, 1977), pneumonia or pneumonia infiltrate (Flury et al., 1983; O'Kane, 1983; Hoeffler et al., 1982; Kass et al.,

1972; Osmond and Tallents, 1968; Caplin, 1941; Slot, 1938), chronic infectious lung disease (O'Kane, 1983), and a prolonged decrease in pulmonary function (Price et al., 1983; Birken et al., 1981; Close et al., 1980; Kass et al., 1972).

Reported pathologic findings in deceased victims 2 to 120 days following excessive ammonia inhalation have been loss of cartilage in both lungs (Birken et al., 1981); cystic bronchiectasis (Hoeffler et al., 1982; Birken et al., 1981; Sobonya, 1977); distended, congested lungs (Arwood et al., 1985; Birken et al., 1981; Sobonya, 1977; Walton, 1973; Caplin, 1941; Slot, 1938); denudation of epithelium from bronchial walls (Arwood et al., 1985; Burns et al., 1983; Sobonya, 1977; Walton, 1973; Caplin, 1941); edema (Burns et al., 1983; Walton, 1973; Caplin, 1941; Slot, 1938); bronchopleural fistula, thickened bronchial walls, fibrous tissue growths (Sobonya, 1977), and hemorrhage (Burns et al., 1983).

3.10.3 *Burns of the Skin*

Chemical burns of the skin constitute the remaining major consequence of accidental exposure to high concentrations of ammonia. Upon contact with the skin, ammonia forms ammonium hydroxide, which causes burns similar to those caused by other alkalies. A concentration of 7,070 mg/m^3 (10,000 ppm) is sufficient to evoke skin damage (Birken et al., 1981). The maximal concentration of vapor tolerated by the skin for more than a few seconds is 14,140 mg/m^3 (20,000 ppm), whereas 21,210 mg/m^3 (30,000 ppm) may produce blisters in a few minutes (National Research Council, 1977). Several case reports of chemical burns as a result of acute exposure have been reported (Flury et al., 1983; Close et al., 1980; Hatton et al., 1979; Walton, 1973; Kass et al., 1972; Helmers et al., 1971; Osmond and Tallents, 1968; Levy et al., 1964; Slot, 1938).

3.10.4 *Other Effects*

Chronic exposure to 28 mg/m^3 (40 ppm) ammonia vapor has resulted in headache, nausea, and reduced appetite (National Research Council, 1977). Other reported effects of exposure to ammonia vapor are convulsions (Kass et al., 1972), shock (Osmond and Tallents, 1968; Slot, 1938), gastritis (Dupuy et al., 1968; Slot, 1938), urticaria (Morris, 1956), leukocytosis (Ward et al., 1983), and inflammatory bronchoconstriction (Bernstein, 1982). Herrick and Herrick (1983) described a case of allergic reaction in a female weight lifter who inhaled an aromatic ammonia inhalant. Shortly after inhalation, the woman presented with rhinitis, rhinorrhea, conjunctivitis, dizziness, headache, dyspnea, wheezing, periorbital swelling, and urticaria. Ingestion of ammonia (usually in the form of household ammonia, a 1.5 M solution of 28 percent ammonia) has resulted in acute corrosive esophagitis and gastritis followed by esophageal and gastric stenosis (Ernst et al., 1963; Norton, 1960).

Shimkin et al. (1954) reported a case in which epidermoid carcinoma of the upper lip was diagnosed 2 months after the patient spilled an oil-ammonia mixture on the area. The authors suggested that the case was "acceptable as an instance of a single-exposure, chemical-trauma exteriorization of a latent cutaneous carcinoma in man." However, no similar reports were found in the available literature.

3.10.5 *Experimental Studies*

Several studies have been carried out in human subjects exposed to low levels of ammonia. Schmidt and Vallencourt (1948) exposed one subject

(Schmidt) to 375 to 396 mg/m^3 (530 to 560 ppm) of ammonia for 4 hours and found no significant changes in the pulse, pH, urea and creatinine levels, or CO_2-binding power (the amount of CO_2 that can exist in serum or plasma as HCO_3^- at a PCO_2 of 40 mm Hg) of the blood over the exposure period. The systolic blood pressure stayed constant for the first 35 minutes of exposure, then decreased from 127 mm Hg at 35 minutes to 102 mmHg at 180 minutes. There was a marked linear increase in nonprotein nitrogen from 27 to 57 mg% at 4 hours when exposure was ended. After termination of exposure, nonprotein nitrogen levels decreased linearly, approaching the preexposure level 3 hours after exposure cessation. However, later studies disputed these findings; i.e., the reported blood nitrogen levels reached 36.4 mg% after 4 hours, exceeded maximum theoretical retention levels (Silverman et al., 1949) and were inordinately higher than levels sufficient to induce death in rats and rabbits (Ting, 1950).

In a study by Silverman et al. (1949), all exposed persons (7) experienced hyperventilation ranging from 150 to 250 percent above normal values after being exposed to 354 mg/m^3 (500 ppm) ammonia for 30 minutes. Lacrimation and nasal irritation were noted in two subjects. No changes were observed in blood urea, nonprotein nitrogen, or CO_2-binding power in two subjects tested. In one of the two subjects, a slight elevation in pulse and blood pressure was noted.

Verberk (1977) exposed 16 volunteers to 42, 57, 78, and 99 mg/m^3 (60, 80, 110, and 140 ppm) ammonia for 2 hours at each exposure level over a 4-week period. The subjects consisted of eight "experts" persons familiar with the effects of ammonia, and eight "students," persons who were not. No changes in vital capacity, forced expiratory volume, or forced inspiratory volume were noted. The "students" were more responsive than the "experts" for subjective effects, e.g., smell, irritation of the eyes, throat, or nose, urge to cough, and general discomfort. The effect of ammonia exposure on "students" seemed to be concentration-dependent.

In another study with six volunteers, two subjects were exposed to 18, 35 or 71 mg/m^3 (25, 50, or 100 ppm) ammonia for 6-hour sessions once a week for 6 weeks (Ferguson et al., 1977). No apparent changes in respiration rate, blood pressure, pulse, or forced vital capacity were noted. An increase in the 1-second forced expiratory volume occurred with increasing concentrations. The frequency of mild eye irritation decreased in the later sessions, suggesting an adaptation to the exposure. However, the authors stated that the exposure concentrations were not constant, with excursions to 106 to 141 mg/m^3 (150 to 200 ppm) occurring, which produced lacrimation and transient discomfort.

Cole et al. (1977) examined minute volume, tidal volume, and heart rate during submaximal exercise in 18 male volunteers exposed to ammonia. The exposure took place in two periods during which the volunteers exercised at 20 to 120 W for 8 minutes and 20 to 180 W for 11 minutes. The exposure level was 50 to 79 mg/m^3 (71 to 113 ppm) ammonia gas for the first period and 115 to 158 mg/m^3 (165 to 226 ppm) for the second period. Reported subjective responses consisted of a prickling sensation in the nose and a slight dryness of the mouth but no real discomfort. There was no significant difference in heart rate, but there were significant decreases ($p < 0.05$) in minute volume (from 25 to 22.5 liters/minute), tidal volume (from 1.57 to 1.43 liters), and an increase in mean respiratory frequency (from 19.1 to 21.0 breaths/minute) with exposure at the higher level. There were no significant changes in these parameters with exposure at the lower level (50 to 79 mg/m^3). The authors suggested that the ventilatory responses to ammonia

occurred a few minutes after exposure onset and were reversible, indicating a reflex rather than a structural reaction.

Eleven of 23 subjects complained of nasal irritation after exposure to 71 mg/m^3 ammonia for up to 30 seconds in each nostril (McLean et al., 1979). All of the subjects showed increased nasal airway resistance, which was suspected to be due to vascular dilation in the nasal mucosa, and/or edema resulting from increased vessel permeability.

In a study by an independent testing laboratory reported in Johnston et al., (1979), 10 subjects were sequentially exposed for 5-minute intervals to 23, 35, 51, and 95 mg/m^3 (32, 50, 72, and 134 ppm) ammonia. At 23 and 35 mg/m^3, 1 of 10 and 2 of 10, respectively, noted dryness of the nose. At 51 mg/m^3 eye irritation (3 of 20), nasal irritation (2 of 10), and throat irritation (3 of 10) were experienced. At 95 mg/m^3, lacrimation accompanied by eye irritation (5 of 10), nasal irritation (7 of 10), throat irritation (8 of 10), and chest discomfort (1 of 10) were reported by the subjects. These subjective symptoms were the only effects investigated. The laboratory workers concluded that concentrations of 35 mg/m^3 or less did not cause irritation or discomfort.

Increased incidences of upper respiratory tract disease, skin changes, and alterations in lipoprotein and protein metabolism were reported in 140 adolescents exposed to ammonia and nitrogen oxides for 3 hours/day for 2 to 3 years while enrolled in a vocational training program, when compared to a control group. However, the exposure concentrations were reported as "not exceeding maximal permissible concentrations," and it was not stated whether these increased incidences were statistically significant (National Research Council, 1977).

Donham et al. (1984) evaluated the acute respiratory effects of the work environment in swine confinement workers. Workers were selected from 21 swine confinement operations with a history of spending at least 5 hours/day in the buildings. Controls were nonsmoking office workers and students with no previous occupational exposure to swine confinement and no history of chronic respiratory disease. Both groups were subjected to a 4-hour exposure period inside a swine confinement building for two separate exposures. Pulmonary function tests were taken immediately before and after exposure. A decrease in FEV_1, FVC, FEV_1/FVC, and FEF_{25-75} was seen in all exposed subjects. However, a greater decrease in the pulmonary function parameters was seen in the swine confinement workers. Further, these effects were more significant in workers that had been employed in the swine confinement operation for >6 years compared to workers employed for <6 years. The levels of respiratory irritants found in the swine confinement building were not given; however, levels of ammonia ranging from 14 to 30 mg/m^3 (20.3 to 42.2 ppm) in addition to high levels of other respiratory irritants in swine confinement buildings have recently been reported by Donham and Popendorf (1985).

3.10.6 *Epidemiology*

The earlier data on the adverse effects associated with chronic occupational exposure to ammonia have been discussed by the National Research Council (1977) and Carson et al. (1981). Most of these studies involve chronic exposure to a mixture of substances and lack adequate experimental design to abstract any meaningful information. More recently, in a case control study of renal cancer mortality at a Texas chemical plant, an increased incidence of renal cancer mortality from exposure to a variety of

physical agent exposures for 26 former employees deceased of renal cancer and two matched control groups. There was however, an elevated risk for "chlorine" workers but those workers were exposed to other compounds as well (Bond et al., 1985).

There are no adequate epidemiology studies or animal carcinogenicity studies for ammonia in the present data base. However, since ammonia is a key metabolite in mammals and plays an essential role in acid-base regulation and in the biosynthesis of purines, pyrimidines and nonessential amino acids, it is unlikely that ammonia is a human carcinogen. Comprehensive assays however, have not been done and therefore, ammonia should be classified as group D "not classifiable as to human carcinogenicity" based on the weight-of-evidence approach in the current EPA guidelines for carcinogen risk assessment.

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